REMARKS/ARGUMENTS

Claims 1, 5-7, 9, 11-14, 16-19 and 105-112 are active in this case.

Support for the definitions of G-CSF and Claims 106-112 is found in the specification on pages 20-25.

Applicants thank Examiners Borgeest and Kemmerer for the courtesy of discussing the issues raised in the Official Action in this application and the issues raised in the Official Action raised in the related 10/880,101 application with their undersigned representative on December 4, 2007. With respect to the present application, the substance of the discussion is summarized and expanded upon in the remarks below.

During this meeting, the rejection under 35 USC 102(e) based on Chajut was discussed.

As explained previously, Chajut was filed on June 7, 2002 with a claim of benefit to a provisional application filed on June 7, 2001. As explained in the Rule 131 Declaration previously made of record, prior to June 7, 2001 certain named inventors had conceived and reduced to practice the invention using G-CSF for the treatment of traumatic brain injury described and claimed in the above-identified U.S. Patent Application. Indeed, this is consistent with the law and guidance provided in MPEP 136.05 Overcoming a Rejection Under 35 U.S.C. 102(e):" A 35 U.S.C. 102(e) REJECTION CAN BE OVERCOME BY ANTEDATING THE FILING DATE."

The Action, while acknowledging this, stated that the rejection would be maintained because the only way to resolve this was an interference. While Applicants disagree as explained during the above-noted meeting, the application of Chajut was abandoned with no further continuing applications having been filed. Screen shots from the USPTO Public

PAIR system indicating that the status of the Chajut application as abandoned and the absence of continuing applications are provided below.

10/165,350	Methods of using colony stimulating factors in the treatment of tissue damage and ischemia		01-10-2008::15:39:35
Bibliographic Data			
Application Number:	10/165,350	Customer Number:	-
Filing or 371 (c) Date:	06-07-2002	Status:	Abandoned -- Failure to Respond to an Office Action
Application Type:	Utility	Status Date:	08-23-2004
Examiner Name:	HAMUD, FOZIA M	Location:	ELECTRONIC
Group Art Unit:	1647	Location Date:	-
Confirmation Number:	4388	Earliest Publication No:	US 2002-0198150 A1
Attorney Docket Number:	2094/65245-A/JPW/FHB	Earliest Publication Date:	12-26-2002
Class / Subclass:	424/085.200	Patent Number:	-
First Named Inventor:	Ayelet Chajut , Ramat Hasharon, (IL)	Issue Date of Patent:	-
Title of Invention:	Methods of using colony stimulating factors in the treatment of tissue damage and ischemia		

10/165,350	Methods of using colony stimulating factors in the treatment of tissue damage and ischemia			01-10-2008::15:40:13
Parent Continuity Data				
Description	**Parent Number**	**Parent Filing or 371 (c) Date**	**Parent Status**	**Patent Number**
This application Claims Priority from Provisional Application	60/296,585	06-07-2001	Expired	-
Child Continuity Data				
No Child Continuity Data Found				

Reconsideration of whether Chajut is actually applicable prior art is requested. Withdrawal of the rejection is requested.

The rejection under 35 USC 103(a) based on the combination of Buschmann and Bouma was also discussed with the recognition that the other obviousness rejections including Siren, Zoppo, Emerich, Tarkowski, and/or Lu fall as well once it is understood that the combination of Buschmann and Bouma do not teach that which is claimed.

During the discussion, the undersigned explained that one would not have had a reasonable predictability in treating tramautic brain injury based on what is described in the cited art. In support, thereof, a Declaration from Professor Kuschinsky of the University of Heidelberg is attached to explain why this is so.

As explained by Professor Kuschinsky, one would not have combined the knowledge in Bouma and WO 99/17798 due to the very different time windows underlying the conditions each sought to treat and indeed would lead one away from treating traumatic brain injury with G-CSF as described in the current application.

This conclusion is based on the fact that Bouma teaches that traumatic brain injury is accompanied by an early and transient ischemic event a few hours after head injury (see Bouma p. 366, left column: "*Recently, however, we have found evidence that ischemia ... if present, only occurs in the first few hours after severe head injury, while after 24 hours the mean CBF [, cerebral blood flow,] usually has increased to values suggestive of 'relative hyperemia' ...*" and "*... confirming the hypothesis that posttraumatic ischemia is usually an early event ...*" and "*In our earlier study, the 33 % incidence of ischemia found between 4 and 6 hours postinjury rapidly decreased with time ...*").

On the other hand the stimulation of arteriogenesis according to WO 99/17798 is a comparably slow process which needs several days up to few weeks to develop. The WO 99/17798 patent application itself reports the enhanced growth of collateral arteries within 7 days (see the description of the femor ligation experiment in Example 1).

Said another way, traumatic brain injury induced ischemia as discussed by Bouma et al has already ended when the WO 99/17798 teachings for arteriogeneiss begins.

The attached publications, discussed below, provide further basis for the timing at which traumatic brain injury induced ischemia begins when compared to arteriogenesis.

1. Paskins-Hurlburt et al. (1992) *Cir. Res.*70(3):546-553 report that more than 1 week is needed for the growth of collateral arteries (see page 550, left column "*... the collateral arteries were inadequate at 1 week. At that time they would not support muscle work, and basal and peak blood flow were reduced. Skeletal*

muscle contractile responses and blood flow, however, clearly had returned to normal by 3 weeks after superficial femoral artery ligation.").

2. Buschmann et al (2001) *Atherosclerosis* 159: 343-356 report the growth of collateral arteries with and without GMCSF administration 7 days after the ligation event. (see abstract: "*The continuous infusion of GM-CSF for 7 days into the proximal stump of the acutely occluded femoral artery of rabbits by osmotic minipump produced indeed a marked arteriogenic response* ...").
3. Hoefer et al (2001) *Cardiovascular Res.* 49:609-617 report the growth of collateral arteries with MCP-1 within 1 week (see p. 615 right column: "Our main finding is that collateral artery growth proceeds in two phases: an early phase with recruitment of numerous pre-existing arterioles which significantly increase conductance within 7 days ...").
4. Herzog et al. (2002) *Am J. Phsiol Heart Cir. Physiol.* 283:H2012-H2020 report the development of collateral arteries within 1 to 2 weeks (see p. H2018, left column: "... studies on acute coronary occlusions have shown that collateral arteries grow within 1-2 wk in a majority of patients.").

Professor Kuschinsky states that what this collective information provides, and also one with relevant knowledge and experience in this field, is that G-CSF would be a candidate for treating traumatic brain injury. Indeed, Professor Kuschinsky would not consider stimulation of arteriogenesis to treat a transient ischemia occurring only hours after the injury not for the treatment of traumatic brain injury as defined by the claims of the application here.

That the application describes both a neuroprotective effect and neuroregenerative effect provides, for the first time a real avenue into treating traumatic brain injury. Without these data, presented in the application, Professor Kuschinsky would not have had an reason

to try using G-CSF for treating traumatic brain injury nor any expectation that such a regimen would work.

Withdrawal of the rejection is requested.

The rejection under 35 USC 112, first paragraph was also discussed.

Granulocyte-colony stimulating factor (GCSF) is a well known growth factor. The structure of both the coding DNA and protein are known as well as methods for recombinantly producing mammalian pluripotent granulocyte colony-stimulating factor (WO 87/01132; U.S. Patent 4,810,643). For example, several amino acid sequences from different species are displayed below in alignment form (showing human, rat, mouse, feline, bovine, and porcine sequences, FIG. 10 from 10/880,101). Indeed, an alignment of just the mouse and human sequences shows that these sequences have about 71.1% identity using a FASTA protein:protein alignment.

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Waterman-Eggert score: 928;  197.3 bits; E(1) <  1.7e-55
71.1% identity (85.3% similar) in 211 aa overlap (1-205:1-208)
Entrez Lookup  Re-search database  General re-search
                10        20        30              40        50        60        70
QUERY   MAGPATQSPMKLMALQLLLWHSALWTVQEATPL------GPASSLPQSFLLKCLEQVRKIQGDGAALQEKLVSECATYKL
        ::  ..:  :::::::::::.::::. .::.::       :.  ::.::::: ::::::::..:..: :.:   ::::::
QUERY   MAQLSAQRRMKLMALQLLLWQSALWSGREAVPLVTVSALPPSLPLPRSFLLKSLEQVRKIQASGSVLLEQL---CATYKL
                10        20        30        40        50        60        70

            80        90       100       110       120       130       140       150
QUERY   CHPEELVLLGHSLGIPWAPLSSCPSQALQLAGCLSQLHSGLFLYQGLLQALEGISPELGPTLDTLQLDVADFATTIWQQM
        :::::::::::::::: : ::.: ::::: . ::::::::: ::::::::: :::: :.:::: ::::::.:::::::::
QUERY   CHPEELVLLGHSLGIPKASLSGCSSQALQQTQCLSQLHSGLCLYQGLLQALSGISPALAPTLDLLQLDVANFATTIWQQM
         80        90       100       110       120       130       140       150

           160       170       180       190       200
QUERY   EELGMAPALQPTQGAMPAFASAFQRRAGGVLVASHLQSFLEVSYRVLRHLA
        :.::.::..::::.:::::.:::::::::::. :.::.:::..  .:.:::
QUERY   ENLGVAPTVQPTQSAMPAFTSAFQRRAGGVLAISYLQGFLETARLALHHLA
        160       170       180       190       200
```

```
1    M A G P A T Q S P M K L M A L Q L L L W H S A L W T V Q E A   hum G-CSF
1    M A Q L S A Q R R M K L M A L Q L L L W Q S A L W S G R E A   mouse G-CS
1    - - - - - - - - - M K L M A L Q L L L W H S A L W S G Q E A   rat G-CSF
1    - - - - - - - - - - K L M A L Q L L L W H S A L W M V Q E A   feline G-C
1    - - - - - - - - - M K L M V L Q L L L W H S A L W T V H E A   bovine G-C
1    - - - - - - - - - M K L M A L Q L L L W H I A L W M V P E A   pig G-CSF

31   T P L G P A S S L P - - - - - - Q S F L L K C L E Q V R K I   hum G-CSF
31   V P L V T V S A L P P S L P L P R S F L L K S L E Q V R K I   mouse G-CS
22   I P L L T V S S L P P S L P L P R S F L L K S L E Q V R K I   rat G-CSF
21   T P L G P T S S L P - - - - - - Q S F L L K C L E Q V R K V   feline G-C
22   T P L G P A R S L P - - - - - - Q S F L L K C L E Q V R K I   bovine G-C
22   A P L S P A S S L P - - - - - - Q S F L L K C L E Q V R K I   pig G-CSF

55   Q G D G A A L Q E K L V S E C A T Y K L C H P E E L V L L G   hum G-CSF
61   Q A S G S V L L E Q L - - - C A T Y K L C H P E E L V L L G   mouse G-CS
52   Q A R N T E L L E Q L - - - C A T Y K L C H P E E L V L F G   rat G-CSF
45   Q A D G T A L Q E R L - - - C A A H K L C H P E E L V L L G   feline G-C
46   Q A D G A E L Q E R L - - - C A A H K L C H P E E L M L L R   bovine G-C
46   Q A D G A E L Q E R L - - - C A T H K L C H P Q E L V L L G   pig G-CSF

85   H S L G I P W A P L S S C P S Q A L Q L A G C L S Q L H S G   hum G-CSF
88   H S L G I P K A S L S G C S S Q A L Q Q T Q C L S Q L H S G   mouse G-CS
79   H S L G I P K A S L S S C S S Q A L Q Q T K C L S Q L H S G   rat G-CSF
72   H A L G I P Q A P L S S C S S Q A L Q L T G C L R Q L H S G   feline G-C
73   H S L G I P Q A P L S S C S S Q S L Q L T S C L N Q L H G G   bovine G-C
73   H S L G L P Q A S L S S C S S Q A L Q L T G C L N Q L H G G   pig G-CSF

115  L F L Y Q G L L Q A L E G I S P E L G P T L D T L Q L D V A   hum G-CSF
118  L C L Y Q G L L Q A L S G I S P A L A P T L D L L Q L D V A   mouse G-CS
109  L F L Y Q G L L Q A L A G I S S E L A P T L D M L H L D V D   rat G-CSF
102  L F L Y Q G L L Q A L A G I S P E L A P T L D M L Q L D I T   feline G-C
103  L F L Y Q G L L Q A L A G I S P E L A P T L D T L Q L D V T   bovine G-C
103  L V L Y Q G L L Q A L A G I S P E L A P A L D I L Q L D V T   pig G-CSF

145  D F A T T I W Q Q M E E L G M A P A L Q P T Q G A M P A F A   hum G-CSF
148  N F A T T I W Q Q M E N L G V A P T V Q P T Q S A M P A F T   mouse G-CS
139  N F A T T I W Q Q M E S L G V A P T V Q P T Q S T M P I F T   rat G-CSF
132  D F A I N I W Q Q M E D V G M A P A V P P T Q G T M P T F T   feline G-C
133  D F A T N I W L Q M E D L G A A P A V Q P T Q G A M P T F T   bovine G-C
133  D L A T N I W L Q M E D L R M A P A S L P T Q G T V P T F T   pig G-CSF

175  S A F Q R R A G G V L V A S H L Q S F L E V S Y R V L R H L   hum G-CSF
178  S A F Q R R A G G V L A I S Y L Q G F L E T A R L A L H H L   mouse G-CS
169  S A F Q R R A G G V L V T S Y L Q S F L E T A H H A L H H L   rat G-CSF
162  S A F Q R R A G G T L V A S N L Q S F L E V A Y R A L R H F   feline G-C
163  S A F Q R R A G G V L V A S Q L H R F L E L A Y R G L R Y L   bovine G-C
163  S A F Q R R A G G V L V V S Q L Q S F L E L A Y R V L R Y L   pig G-CSF

205  A Q P                                                         hum G-CSF
208  A .                                                           mouse G-CS
199  P R P A Q K H F P E S L F I S I .                             rat G-CSF
192  T K P                                                         feline G-C
193  A E P                                                         bovine G-C
193  A E P                                                         pig G-CSF
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Therefore, mammalian G-CSF, human G-CSF, a protein having at least 90% homology to SEQ ID NO:28 and G-CSF activity are described by what is provided in the

specification and the knowledge in the field. (see *Capon v. Eshhar* (Fed. Cir. 2005): "When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh."; see also *Falkner v. Inglis,* 79 USPQ2d 1001 (Fed. Cir. 2006): "Recitation of Known Structure Is Not Required" to satisfy written description requirement).

Making fusion proteins with such known sequences is also provided in the specification (see, e.g., pages 47-48). Therefore, the limitation of mammalian or human G-CSF fused to a second protein is described.

Modifying a primary amino acid sequence with chemical substituents is also a known entity (see, e.g., page 46 of the application). Therefore, the limitation of mammalian or human G-CSF comprising one or more chemical substituents is described.

Accordingly, withdrawal of the rejection is requested.

To the provisional obviousness double patenting rejection in view of claims 1-5, 9-22 and 52-53 of co-pending application no. 10/880,101. The claims here are for treating traumatic brain injury whereas the now pending claims of the 10/880,101 are for treating peripheral neuropathy. Treating one condition does not necessarily result in treating the other condition and vice versa nor would it be obvious to do so.

Withdrawal of the rejection is requested.

A Notice of Allowance is also requested.

Respectfully submitted,

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